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AN INVESTIGATION INTO THE GENETIC BACKGROUND  
OF PERNICIOUS ANEMIA BY AN IMMUNOLOGICAL METHOD

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In a group of 120 pernicious anemia patients antiparietal cell antibodies were found in 104 (87%) by means of the indirect immuno-fluorescence technique of Coons and Kaplan. These antibodies, which could be localized in the 7S gamma globulin fraction, were understood as auto-antibodies; they appear, in view of the high frequency with which they occur in cases of pernicious anemia, to be an essential manifestation of it. The corresponding antigen was localized by absorption techniques in the microsome fraction of a stomach homogenate.

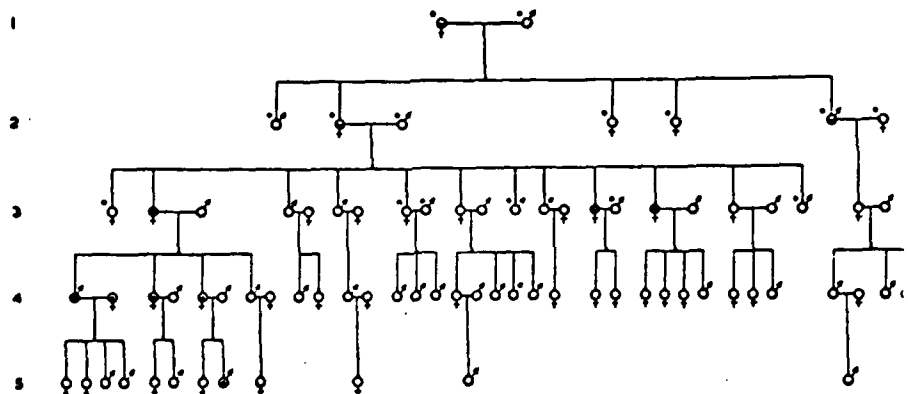
A study of the presence of antiparietal cell antibodies in members of the families of patients suffering with pernicious anemia produced a 20% positive result. On the basis of a clinical study of relatives with antibodies it appeared that the presence of the antibody may be thought of as an early symptom of a future gastritis; in the presence of antibody in relatives with no functional or morphological changes in the mucous membrane of the stomach an indication was found for atrophic gastritis as a basis for the auto-immune genesis of pernicious anemia. There are arguments for thinking in this connection principally of a "delayed type" hypersensitivity. At the same time it appeared that a study of the occurrence of this antibody as a part of a hereditability study would produce more information than a study of the occurrence of achlorhydria or diminished vitamin B<sub>12</sub> resorption (see the table).

That this study of the occurrence of parietal cell antibodies in relatives of patients with pernicious anemia actually constitutes a study of a hereditarily determined fac-

TABLE

Family Mem- bers with Anti- Parietal Cell Antibodies	No	Stomach Fundus Biopsy		van Schilling Test 48-Hour Secretion of $^{58}\text{Co}$ vit. B-12			Stomach-Acid Secre- tion After Histamine Stimulation	
		Normal	Gastritis	< 10	10-20	> 20	Negative	Positive
Brothers and Sisters	7	1	6	3	2	2	4	3
Children	5	1	4		1	4	2	3
Nephews and Nieces	2	1	1		1	1	1	1
Total	14	3	11	3	4	7	7	7

tor became evident from the fact that the sera of 216 relatives of patients with pernicious anemia reacted positively to pernicious anemia in 20% of the cases; in a control group consisting of 76 relatives by marriage the figure was only 3%. An analysis of the family tree also told in favor of this view (see the family tree).



● = pernicious anemia    • = anti-parietal cell antibodies    ◐ = possible pernicious anemia    \* = deceased

The pattern of inheritance of the antiparietal cell antibodies is marked: a) by the occurrence of antibody in a direct line in the succeeding generations; b) by the absence of antibody in the posterity of family members without antibodies; c) by the fact that two parents with antibodies can have children without antibodies. These data indicate that the occurrence of antibody is determined by a dominant gene in a heterozygote carrier. An analysis of the available data by the method of maximum "likelihood" was in agreement with this view. In view of the absence of antibody in 13% of those suffering from pernicious anemia, the penetrance of

the gene is thus not complete. If we conceive of the characteristics of pernicious anemia as derived from various genes with a pleiotropic pattern that is controlled by one dominant gene, the most complete manifestation of that gene will be the form of pernicious anemia in which the antibody is demonstrable.

It can thus be said that the occurrence of antiparietal cell antibodies and so of the purest form of pernicious anemia is bound to a dominant gene with a heterozygotic carrier. In a number of the relatives and in the impure form of pernicious anemia the gene shows a reduced penetrance. As no difference in occurrence of the antiparietal cell antibodies can be shown between the sexes, the gene must be autosomal.

The knowledge that the occurrence of pernicious anemia in a number of the relatives is a question of time and circumstances on the one hand and the possibility of detecting these relatives for the most part by means of a very simple method on the other hand bring up the question to what extent preventive measures can be taken. In our opinion all relatives above thirty years old with antibodies must be examined for the presence of the intrinsic factor in the gastric juice; in its absence they must be treated with vitamin B<sub>12</sub> before deficiency symptoms appear.

Discussion:

Sangster: Among the three patients with unfavorable van Schilling tests were there persons with free acid in the gastric juice?

Te Velde answers in the negative.